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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,695	11/21/2006	Toshihiro Tanaka	P29373	4545

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EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
10/14/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/568,695	TANAKA ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1 and 5-13* is/are pending in the application.

5a) Of the above claim(s) *5-13* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 5-13 are pending.

Claims 5-13 remain withdrawn from examination as detailed in the Office Action of 01/26/2009.

Claim 1 is examined on the merits.

This Office Action is in reply to Applicants' correspondence of 07/25/2011.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL**.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Enablement

1. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The instant claims are drawn to methods for determining an increased risk of myocardial infarction in humans.

The claims require knowledge of a correlative association between a C at position 3279 of SEQ ID NO: 1 and an increased risk of myocardial infarction.

Direction provided by the specification and working example

The specification provides an example of the identification of a polymorphism in the human galectin-2 gene, where the polymorphic content is either a C or a T at position 3279 of SEQ ID NO: 1 (p.6-7).

The specification teaches (p.16; p.20-21), the analysis of the polymorphisms in case and control populations to study the association of the SNP content with the presence of myocardial infarction (MI). The specification asserts that the presence of the TT genotype at the position in both alleles of the galectin-2 gene is indicative of a decreased risk of MI (p.20).

The specification does not provide any examples of the analysis of any other arteriosclerotic diseases other than MI. There is no validation analysis of any additional population other than the subjects as presented in Table 1 on page 21 of the specification.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to the detection of any particular nucleotide sequence is high, the unpredictability with regard to the association of any particular sequence with a particular phenotype, or the identification of any nucleotide sequence has having a particular functionality, is even higher. The unpredictability is demonstrated by the prior art and the post-filing art.

Because the nature of the claimed methods requires knowledge of a robust and reliable association between nucleotide content and disease risk, it is relevant to point out the unpredictable nature of any mutation association study. As evidence of the unpredictability of gene association studies, Lucentini (2004) teaches that it is strikingly

common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). Additionally, Hegele (2002) teaches the general unpredictability in associating any genotype with a phenotype. Hegele teaches that often initial reports of an association are followed by reports of non-replication and refutation (p.1058, right col., lns.24-30). Hegele provides a table indicating some desirable attributes for genetic association studies (p.1060), and includes choosing an appropriate significance threshold (see 'Minimized type 1 error (FP)') and replication of results in independent samples (see 'Replication'). Additionally, Hegele teaches the desirability of a likely functional consequence predicted by a known or putative functional domain.

The unpredictability as generally described by Lucentini and by Hegele, as cited above, is particularly relevant considering the teachings of the post-filing art. For example, the post filing-art teaches the analysis of the same SNP in the galectin-2 gene and a lack of association with MI. Mangino et al (2007) teach that the SNP rs7291467 (the same SNP of the instant application) is not associated with MI in a Caucasian population (p.114 left col.). Similarly, Sedlacek et al (2007) teaches (p.1000, Table 3) that there is no significant association between the same SNP and MI in two German

populations. Finally, Kimura et al teaches that there was no association of the SNP with MI in a Japanese population or a Korean population (p.267, left col.; Table 3). It is thus unpredictable as to weather or not the asserted association of the instant specification would in fact reliably or robustly be reproduced in any other different population.

Additionally, Li et al (2010) provides a meta analysis of all available data, in numerous diverse study population, related to the galectin-2 3279 SNP and heart disease. The reference concludes (e.g.: Figures 4 and 5) that there is no statistically significant, reliable association between the 3279 SNP content and heart disease risk (e.g.: p.434 - Results).

Quantity of experimentation required

A large and prohibitive amount of experimentation would have to be performed in order to make and use the claimed invention. Such experimentation would include large case:control studies to establish whether or not the asserted associations are reliable and robust in any subject population of interest. Such experimentation would be extensive. Even if one were to carry out such experimentation, there is no assurance that a reliable and consistent association of genetic content with MI would be identified.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments and analysis of the data presented in the cited references (p.2-8 of the Remarks of 07/25/2011) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection. Applicants have continued to argue that the various cited references are flawed for various reasons, and thus do not support the conclusion of lack of enablement. The Examiner maintains that the cited references are published in peer reviewed journals, and in so far as the Office itself does not maintain laboratories to perform scientific analysis, the cited references are accepted for what they appear to teach. And while Applicants assert that the references use populations that are smaller than those disclosed in the instant specification, or populations that are genetically diverse, or particular to an ancestral group, each reference as cited comes to the conclusion that there is a lack of a reliable association between the SNP required in the claims and the cardiovascular disease phenotype. Thus the Examiner maintains that while a study of a cited reference may use a smaller population than the analysis of the instant specification, the study of the cited reference still is able to perform a valid statistical analysis that shows a lack of association. And where the cited art may look at different populations (e.g.: a genetically diverse population; or a particular different ancestral population), such analyses still speak to the unpredictability in reliably associating genotype with phenotype. Furthermore, Applicants analysis (pages 6-7 of Remarks of 07/25/2011) of the full data as presented in the meta analysis of Li et al is not persuasive to withdraw

the rejection. Where Li et al teaches that, in the bi-allelic T/C SNP, there is no association between the T-allele and MI, the examiner maintains that such a conclusion is extremely relevant to the instant claims even though the claims are drawn to detection of a C-allele. It is noted that Li et al fails to find a significant protective influence of the T-allele in either a dominant (Fig. 4) or recessive (Fig 5) model. And Applicants analysis of the data appear to self-support the Examiners conclusion of a high level of unpredictability and lack of enablement. Table 2 of the Remarks appear to indicate only a significant association when the TT genotype is compared to other genotypes (i.e.: CT and CC), however the same table shows a less than significant association when the CC genotype s compared to the CT and TT genotypes. Table 3 of the remarks shows a less than significant relationship when the TT genotype is compared to other genotypes, and while applicants argue 'these values imply that significance might arise if the number of samples increases', the Examiner maintains that an increase in the number of samples (such as with the meta-analysis of Li et al) could just as likely indicate that there is not a significant association. The Examiner maintains the position that when the available evidence is taken together, the evidence does not support the required association.

The rejection as set forth is **MAINTAINED.**

Conclusion

2. No claim is allowed.

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634